REMARKS/ARGUMENTS

Applicants' counsel thanks Examiner Lucas for his continued careful and thorough examination of the present application and for his comments provided in the Advisory Action dated May 22, 2009. Applicant's counsel also thanks Examiner Lucas for granting a telephone interview on June 11, 2009, during which claims 1 and 9 were discussed with regard to the Wechter reference. Also discussed was amendment of claim 1 based on replacing "combining" with "mixing," evidence based on scientific publications, and Applicant's argument that Wechter teaches incorporation of antigens derived from virus, not incorporation of live virus per se, into iscoms, for example based on the teaching of a reference to Fohlman cited by Wechter and based on the meaning of iscom terminology regarding incorporation. Applicant's counsel indicated that Applicant planned to file a Request for Continued Examination. It is believed that the Amendment the Claims and Remarks address the corresponding instructions of the Examiner.

I. FORMAL MATTERS

A. RCE and request not to enter previously filed unentered Amendment

Applicant respectfully instructs the Examiner not to enter the unentered Amendment to the Claims and the Remarks previously filed on May 18, 2009. Applicant also respectfully instructs the Examiner not to enter the unentered Declaration of Morein and accompanying Exhibits A, B, C, and D previously filed on May 18, 2009.

B. Other formal matters

Applicant continues to acknowledge that the Examiner has withdrawn the species elections with regard to Fraction A and Fraction C of Quillaja Saponaria Molina and that claims

3, 11, 16, 17, and 19 are withdrawn. Applicant notes again that claims 3 and 11 depend from claims 1 and 9, respectively. Accordingly, on allowance of claims 1 and 9, rejoinder and allowance of the claims 3 and 11 is respectfully requested pursuant to the Office's rejoinder procedure. MPEP § 821.04.

Applicant acknowledges that the Examiner has withdrawn the prior rejection of claims 1, 2, 4-7, and 18 under 35 U.S.C. § 112 for indefiniteness and has withdrawn the prior rejection of claims 1, 2, 6, 7, 8, and 18 under 35 U.S.C. § 102(b) as being anticipated by the Iosef reference (Vaccine 20:1740-53).

Claims 1, 7, 8, 13, 14, 22, and 23 have been amended and new claims 24-26 have been added. No new matter has been entered. Basis for the amendments can be found in the specification as filed as follows.

Regarding claim 1, the application discloses "virus-adjuvant mixtures," wherein the virus is live influenza virus and thus a live micro-organism and the adjuvant is A-matrix and thus includes an iscom particle, the virus-adjuvant mixtures being made by adding an adjuvant formulation to a working dilution of the virus. Paras [0091-0093].

Regarding claims 7, 8, 13, 14, and 22-23, the application discloses saponins derived from raw extract of Quillaja Saponaria Molina. Paras. [0034]-[0038]. More specifically, the application discloses a raw extract from Quillaja Saponaria Molina and the fractions A, B, C, B3, B4, B4B and QA1-22 thereof. Paras. [0034-0038]. The application also discloses that saponins of the raw extract can be separated into Fraction A and Fraction C, among other fractions. Para. [0035]-[0037]. Such fractions are termed fractions from Quillaja Saponaria Molina. Para. [0038]. Of note, such fractions are also defined in the art as fractions of Quil A. This is evident, for example, from the WO 96/11711 reference to Cox, cited in paragraphs [0035] and [0063] of

the present application. Specifically, the Cox reference states the following: "[S]aponins with useful adjuvant activity have been derived from the South American tree Quillaja saponaria Molina. Saponin from this source was used to isolate a 'homogeneous' fraction denoted 'Quil A' (Dalsgaard, 1974)". WO 96/11711, p. 1, lines 24-27. Moreover, the Cox reference discloses fractions of Quillaja Saponaria Molina, specifically termed fractions B4B, B3, and B2 of Quil A. WO 96/11711, p. 3, lines 5-8.

Further regarding claims 22-23, the application discloses that composition MM703 was prepared by mixing Matrix A and Matrix C, para. [0085], wherein Matrix A corresponds to iscom matrix particles made from Fraction A of Quillaja Saponaria Molina and Matrix C corresponds to iscom matrix particles made from Fraction C of Quillaja Saponaria Molina, para. [0037]. Thus, MM703 comprises a plurality of iscom particles, wherein a first iscom particle includes Fraction A and not Fraction C, and a second iscom particle includes Fraction C and not Fraction A, consistent with claims 22 and 23, as currently amended.

Regarding new claim 24, the application discloses that the composition may be used for humans. Para. [0046]. Regarding new claim 25, the application discloses that formulations including live virus and either iscom A-matrix or iscom B-matrix both provided titres that were ten-fold higher than for the virus control. Para. [0103]. Regarding new claim 26, the application discloses that a surprisingly high number of ferrets that received the live vaccine mixed with either of the two iscom matrix adjuvants responded with higher titres than those receiving non-adjuvanted live vaccine. Para. [0117].

II. REJECTIONS UNDER 35 U.S.C. § 112

The Examiner has maintained the rejection of claims 8 and 14 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as his invention. Specifically, the Examiner has rejected claims 8 and 14 based on lack of clarity regarding the meaning of "Fractions A or C of Quillaja saponin Fraction A." Office action, p. 3. Claims 7 and 13, as amended, are directed to a method and a composition, respectively, wherein the iscom particle comprises at least one glycoside fragment from Quillaja Saponaria Molina. Claims 8 and 14, as amended, are directed to a method and a composition, respectively, wherein the iscom particle comprises at least one of Fraction A and Fraction C of Quillaja Saponaria Molina. The rejection of claims 8 and 14 is therefore respectfully submitted to be overcome.

The Examiner has rejected claims 22 and 23 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as his invention. Specifically, the Examiner has rejected claims 22 and 23 based on lack of clarity regarding the meaning of "different fractions of Quillaja saponin Fraction A." Office action, p. 3. Claims 22 and 23, as amended, are directed to a method and a composition, respectively, wherein the iscom particle comprise various fractions of Quillaja Saponaria Molina. For the reasons indicated above regarding amendment of claims 8 and 14, the rejection of claims 22 and 23 is respectfully submitted to be overcome.

The Examiner has also rejected claims 22 and 23 on the basis that it is not clear what is meant by the claim language "wherein a plurality of the iscom particles comprise different Fractions of Quillaja saponin Fraction A." Specifically, the Examiner has indicated that "[i]t is not clear what is meant by the claim language if the claim is reading on embodiments wherein

the plurality of iscoms each have the same saponins which is made up of different fractions of Quil A . . . , or if the claims are drawn to embodiments wherein the plurality of iscom particles comprise a plurality of iscom particle populations, each comprising a different Fraction of Quil A from the other iscom populations." Office action, p. 4. Claims 22 and 23, as amended, are directed to methods and compositions, respectively, wherein a plurality of the iscom particles comprise a first iscom particle and a second iscom particle, the first iscom particle comprising a first fraction of Quillaja Saponaria Molina and not a second fraction of Quillaja Saponaria Molina, and the second iscom particle comprising the second fraction of Quillaja Saponaria Molina and not the first fraction of Quillaja Saponaria Molina. The rejection of claims 22 and 23 is therefore respectfully submitted to be overcome.

III. REJECTION OF CLAIMS UNDER 35 U.S.C. § 102(b) – WECHTER REFERENCE

The Examiner has maintained the rejection of claims 1, 2, 6, 9, 10, and 15 under 35 U.S.C. § 102(b) as being anticipated by Wechter et al., U.S. Pat. No. 6,177,081. Moreover, the Examiner has extended the rejection to claim 21. Specifically, the Examiner maintains, as stated in the previous Office action, that "Wechter teaches live attenuated viruses for use in vaccines," that "[t]he reference teaches the combination of the attenuated viruses with an iscom," and that "the reference also inherently teaches claim 6" since "iscoms are known in the art to comprise glycosides and lipids." Office action dated December 17, 2008, p. 5; Office action dated July 28, 2008, p. 5. Moreover, in response to the Applicant's assertion that the teachings of Wechter inevitably involve production steps that will kill microorganisms, the Examiner has stated that such an argument is not sufficient where evidence is required. The Examiner has also stated that

Applicant's argument is not consistent with the teachings of Wechter, given that Wechter "specifically indicates that the live viruses can be incorporated into the ISCOMs, and nowhere indicates that the end result would be an inactivated (killed) virus." Office action dated December 17, 2008. The Examiner has further stated that the text following the cited passage of Wechter, specifically the text describing incorporation of viral capsid proteins, relates to subject matter that is distinct from incorporation of live attenuated virus, rather than being an elaboration on the meaning of incorporation of live attenuated virus. Advisory Action, dated May 22, 2009. The Examiner has also further stated that Applicant has presented "no evidence that those in the art would of necessity use a solubilization agent that would kill the microorganism to be incorporated" and that the fact that saponins may kill micro-organisms "may be partially the reason for incorporating the organisms into iscoms." Advisory Action, dated May 22, 2009.

Respectfully, for the reasons below, including new arguments and evidence, the Wechter reference does not teach claims 1, 2, 6, 9, 10, 15, and 21. Specifically, claim 1, as currently amended, is directed to a method of preparing an antigenic composition, based on mixing an iscom particle and at least one living micro-organism, and claim 9 is directed to a composition comprising at least one iscom particle and at least one living micro-organism. In contrast, as previously asserted by Applicant, Wechter teaches the use of a live attenuated virus as a starting material for antigen incorporation into an iscom particle, said use inevitably involving production steps that will kill any virus or other micro-organism, and thus Wechter does not teach any composition that includes an iscom particle and a live micro-organism or any method for making such a composition.

A. Wechter relates to incorporation of antigens derived from solubilized, and thus killed, virus, not incorporation of live attenuated virus per se.

Wechter does not teach the methods or compositions of claims 1 and 9, given that a person of ordinary skill in the art would understand Wechter to teach that antigens derived based on solubilization, and thus killing, of a live attenuated virus can be incorporated into ISCOMs, not that a live virus per se can be incorporated. This conclusion is based, for example, on the opinion of Dr. Jan Fohlman, an independent expert in the fields of microbiology and infectious diseases, as indicated in the accompanying declaration, Fohlman Declaration, para. 11, for the following reasons, supported by numerous items of corroborating evidence, as briefly outlined here and as described in detail below. First, to the extent that terminology similar to that of incorporation of a live virus into an ISCOM particle has been used in the ISCOMs field, the terminology has been used in reference to solubilization and thus killing of a microorganism prior to incorporation, not in reference to incorporation of the microorganism per se. Second, the scientific literature does not apparently contain even a single reference that purports to explain, in either theory or practice, how a live microorganism per se could possibly be incorporated into an ISCOM particle. Third, it is common in the ISCOMs field to use terminology that on its face would seem to refer to an ISCOM particle into which a virus per se had been incorporated but which in fact corresponds to an ISCOM particle into which antigens derived from solubilized viruses have been incorporated, e.g. "influenza-ISCOMs" or "measles virus ISCOMs." Fourth, the context of the paragraph within which the teaching occurs indicates that the teaching relates to incorporation of antigens derived from virus, not incorporation of live virus per se.

i. Terminology regarding incorporation of viruses into ISCOMs, as used in the ISCOMs field, refers to incorporation of antigens derived from solubilized viruses, not incorporation of viruses per se.

A person of ordinary skill in the art would understand Wechter to teach incorporation of antigens from solubilized, and thus killed, virus, not incorporation of live attenuated virus per se, given that similar terminology based on the term "whole virus" as used in the ISCOMs field refers to incorporation of antigens from solubilized virus, not incorporation of the whole virus per se, and given that the term whole virus, as used in the art, includes live virus. Fohlman Decl., para. 1. The meaning of terminology relating to incorporation of whole virus into ISCOMs can be seen, for example, based on corroborating evidence corresponding to the scientific review article of Barr et al., page 14, submitted as Exhibit C of the Fohlman Declaration, which states the following: "One potential problem in the preparation of ISCOMs is the incorporation of unwanted molecules when whole viruses are used. For example, when cell culture-derived HIV-1 virus was purified, solubilized and incorporated into ISCOMs, the major constituent was found to be HLA-DR which was derived from the host cell and forms part of the viral envelope." (Emphasis added). As can be seen, the quoted passage refers to methods for preparing ISCOMs based on use of "whole viruses" including an incorporation step, and thus uses terminology of incorporation of whole viruses into ISCOM particles. The passage elaborates on the meaning of this terminology, specifically by providing an example that indicates that the methods refer to sequential steps of purification of whole virus, solubilization of the virus, and only then incorporation of the now solubilized remnants of the virus. As explained further below in section III.B.ii., solubilization of a virus (or other microorganism), in

the context of incorporation into an ISCOM, relates to a process that destroys the structural integrity of the virus, resulting in killing of the virus. Thus, this passage demonstrates that the terminology of incorporation of whole viruses into ISCOMs, as used in the art, refers not to incorporation of whole viruses per se but rather solubilization, and thus killing of the viruses, followed only then by incorporation into ISCOM particles. Terminology relating to incorporation of live virus is similar to the terminology relating to incorporation of whole virus. This is because the term whole virus, as used in the art, includes live attenuated viruses, as well as inactivated virus. This can be seen, for example, in the document titled Vaccine Development Overview (available at http://www.brown.edu/Courses/Bio_160/Projects1999/vaccineoverview/vaccineoverviewbody.html), accompanying this filing, which states that "[t]here are two classes of a whole organism vaccine – attenuated (live) and inactivated (killed)." Of note, the above-mentioned Barr reference was submitted and accepted for publication on September 22, 1995, Barr reference, page 8, well after the filing date of the earliest application in the chain of applications that ultimately issued as the Wechter patent, the filing date corresponding to March 9, 1994, which argues against the possibility that the terminology of incorporation as used in Wechter relates to some incorporation technology invented subsequent to the writing of the Barr reference. Accordingly, a person of ordinary skill in the art would understand Wechter to refer to solubilization and thus killing of the live virus, followed only then by incorporation. For at least these reasons, Wechter fails to teach any composition that includes an iscom particle and a live virus, or any other live micro-organism, or any method for making such a composition.

ii. The scientific literature does not apparently include any references purporting to explain how a live microorganism per se could be incorporated into an ISCOM particle, despite Wechter's statement that incorporation of a live attenuated virus can be accomplished "using methods well known in the art."

A person of ordinary skill in the art would understand Wechter to teach incorporation of antigens from solubilized, and thus killed, virus, not incorporation of live attenuated virus per se, given that the scientific literature does not apparently include a single reference that purports to explain, in either theory or practice, how a live microorganism per se could be incorporated into an ISCOM particle, whereas the scientific literature includes numerous articles, including review articles, of which the above-mentioned Barr reference is one, that describe methods for incorporating antigens, derived based on solubilization of microorganisms, into ISCOMS. Fohlman Decl., para. 12. This can be seen, for example, based on corroborating evidence corresponding to the accompanying printed results of a PubMed search, conducted on June 14, 2009, based on the search terms "incorporation and live and iscom," filed as Exhibit D of the Fohlman Declaration. As shown in Exhibit D, the search yielded 31 articles. Of note, except as expressly stated, the applicant does not admit as prior art any of the articles identified in any of the PubMed searches discussed herein. As explained in detail in the Fohlman Declaration, none of the 31 articles discloses any method for incorporation of a live microorganism per se into an ISCOM particle. To the extent that any of the articles uses terminology of incorporation of a live microorganism, the terminology is used in relation to solubilization and thus killing of the microorganism, followed by incorporation of the solubilized remnants of the killed microorganism into ISCOM particles. Of note, a search for the term "iscom" alone yielded 472

articles, indicating that the PubMed database includes hundreds of articles that relate to ISCOMs. Fohlman Declaration, Exhibit E (corresponding to the printed results of the first several pages of the search, including the titles of the first 20 articles identified in the search). Of further note, a search for the terms "incorporation and iscom" yielded 276 articles, implying that the PubMed database includes hundreds of articles that relate to incorporation of compounds and structures into ISCOMs. Fohlman Declaration, Exhibit F (corresponding to the printed results of the first several pages of the search, including the titles of the first 20 articles identified in the search). Given the absence of any articles describing incorporation of live microorganisms per se into ISCOMs in the results of the PubMed search based on the search terms "incorporation and live and iscom" and given the multitude of articles relating to ISCOMs and incorporation of compounds therein in the results of the PubMed searches based on the search terms "iscom" and "incorporation and iscom," it is not plausible that Wechter could be understood to indicate that methods for incorporation of live microorganisms per se into ISCOM particles were well known in the art at the time of filing of the Wechter application. Accordingly, a person of ordinary skill in the art would understand Wechter also to refer to solubilization and thus killing of the live virus, followed only then by incorporation. For at least these reasons, Wechter fails to teach any composition that includes an iscom particle and a live virus, or any other live micro-organism, or any method for making such a composition.

iii. Terminology of "virus-ISCOMs" relates to ISCOMs into which antigens derived from viruses, not live or whole viruses per se, have been incorporated, further supporting understanding of the terminology of "incorporation of a live virus" to refer to incorporation of antigens derived from a virus, not incorporation of a virus per se.

A person of ordinary skill in the art would understand Wechter to teach incorporation of antigens from solubilized, and thus killed, virus, not incorporation of live attenuated virus per se, given that it is common in the ISCOMs field to use terminology that on its face would seem to refer to an ISCOM particle into which a virus per se had been incorporated but which in fact corresponds to an ISCOM particle into which antigens derived from solubilized viruses have been incorporated, e.g. "influenza-ISCOMs" or "measles virus ISCOMs." This can be seen, for example, in corroborating evidence corresponding to an accompanying scientific article by Sjölander, S. et al., filed with the Fohlman Declaration as Exhibit G, which refers to "influenza-ISCOMs" and indicates that the influenza-ISCOMs are prepared based on disruption of influenza virus prior to incorporation. Specifically, the Sjölander article, page 4073, indicates that "[i]nfluenza-ISCOMs were prepared as previously described," namely that "to a solution of disrupted A/PR8/34 virus was added a mixture of Quillaia saponin fractions (ISCOPREP(R)703, ISCOTEC AB), cholesterol (Sigma, USA) and di-palmitoyl phosphatidyl choline (Avanti, USA) dissolved in the detergent MEGA-10 (Sigma)." (Emphasis added). This can also be seen, for example, in corroborating evidence corresponding to a scientific article by Stittelaar, K.J. et al., filed with the Fohlman Declaration as Exhibit H, which refers to a "measles virus-iscom," abbreviated as "MV-iscom," and which indicates that the MV-ISCOMs were prepared based on solubilization of the virus prior to incorporation of antigens into the ISCOMs, not based on incorporation of whole or live virus. This can be seen based on the statement in the Stittelaar reference, page 8, that "[t]he iscom-matrixes were prepared identically to the MV-iscoms with the omission of solubilized MV." (Emphasis added). Given that it is common in the ISCOM field to use terminology that on its face would seem to refer to a virus per se incorporated into an ISCOM particle but that actually refers to antigens of solubilized viruses incorporated into

ISCOM particles, again, a person of ordinary skill in the art would understand Wechter also to refer to solubilization and thus killing of the live virus, followed only then by incorporation. For at least these reasons, Wechter fails to teach any composition that includes an iscom particle and a live virus, or any other live micro-organism, or any method for making such a composition.

iv. Context indicates that Wechter teaches incorporation of antigens derived from viruses, not incorporation of live viruses per se.

The context of the paragraph in Wechter within which the teaching regarding incorporation occurs indicates that the teaching relates to incorporation of antigens derived from virus, not incorporation of live virus per se. This conclusion is based, for example, on the opinion of Prof. Bror Morein, an inventor of the present application and discoverer of ISCOMs, for the reasons stated within the Declaration of Morein, para. 11. More particularly, as can be seen, the teaching relates to a general concept, that "[l]ive attenuated viruses can also be incorporated into immunostimulating complexes . . . using methods well known in the art," and occurs in a single sentence. Wechter, col. 9, lines 29-32. The teaching is then followed by a highly specific statement about incorporation, not of live viruses per se, but of viral capsid proteins. Wechter, col. 9, lines 32-35. This form would suggest to a person of ordinary skill in the art that the specific statement provides an example regarding the general statement, rather than representing a change to different subject matter, and thus the general statement, i.e. the teaching, also relates to incorporation, not of live virus per se, but of viral capsid protein. Moreover, the two sentences immediately following the teaching at issue, Wechter, col. 9, lines 32-36, taken together, appear to form a citation to an article, abstract, or book chapter, with the first sentence corresponding to the title and the second sentence corresponding to the first author.

This is apparent for at least two reasons. First, it is typical in the art to provide a citation following a general statement, such as the teaching at issue, that refers to methods well known in the art, so as to direct the reader to an example publication that elaborates on those methods. Indeed, the end of the noted paragraph includes an example of the same. Wechter, col. 9, lines 41-43 ("The methodology for making ISCOM vaccines is well known in the art. (B. Morein, et al., Nature, 308: 457-60, 1984)."). Second, the first of the two sentences is grammatically incorrect in a way that is consistent with the title of an article, abstract, or book chapter, but not a declarative sentence. To the extent that the two sentences correspond to a citation to support the teaching at issue, the citation, based on the title, again would suggest to the person of ordinary skill that the teaching relates to incorporation, not of live virus per se, but of antigens derived from live virus. Of note, searches of the Google and PubMed database did not reveal any publication with this title (see accompanying search results, Google search dated 2009-06-16 and PubMed search dated 2009-06-16). However, the citation to Fohlman apparently corresponds to an article that was authored by the above-mentioned independent expert Fohlman and that does not disclose or relate to incorporation of live viruses per se into ISCOMs. Fohlman Decl., para. 21-22. Although the Examiner has stated in the Advisory Action dated May 22, 2009 that the text following the teaching at issue relates to subject matter that is distinct from incorporation of live attenuated virus, rather than being an elaboration on the meaning of incorporation of live attenuated virus, the above-noted context indicates otherwise. For at least these reasons, Wechter fails to teach any composition that includes an iscom particle and a live virus, or any other live micro-organism, or any method for making such a composition.

B. Incorporation of a live virus or other micro-organism per se into an ISCOM particle is not technologically possible.

Wechter does not teach the methods or compositions of claims 1 and 9, given that it is technically impossible to incorporate a live virus or any other microorganism per se, into an ISCOM particle. This conclusion is based on the opinions of the above-noted Inventor Morein, Morein Declaration, para. 10, and the above-noted independent expert Fohlman, Fohlman Declaration, para. 18, for the following reasons, supported by numerous items of corroborating evidence, as outlined briefly here and as discussed in detail below. First, it would be physically impossible to incorporate any structure as large as a microorganism into an ISCOM particle. Second, the methods that are actually well known in the art for incorporation of compounds or structures into ISCOMs are incompatible with maintenance of the structural integrity of, let alone survival of, any microorganisms.

i. Microorganisms are too large to be incorporated into ISCOM particles, given the size and structure of ISCOMs

The terminology of Wechter regarding incorporation of a live attenuated virus into ISCOMs cannot be a teaching of incorporation of a live attenuated virus per se into an ISCOM particle, because incorporation of any structure as large as a micro-organism into an ISCOM particle is physically impossible due to the size and structure of ISCOM particles. Fohlman Decl. para. 19; Morein Decl. 10. ISCOM particles are small in size, being only about 40 nm in diameter, and have a relatively low internal volume, as can be seen for example based on

evidence corresponding to the above-mentioned Barr reference, which states at page 9 that "[t]ypically ISCOMs and ISCOM matrix particles are hollow, spherical, cage-like particles that have a heterogenous size distribution of around 40 nm in diameter," and which indicates at page 12 that "ISCOMs because of their very small size and internal volume are unable to encase [non-amphipathic] proteins" in the manner of a liposome. The size range of microorganisms is shown, for example, in evidence corresponding to the webpage "Bacteria, Fungi and Viruses, Sizes and Significance," http://www.ionizers.org/Sizes-of-Bacteria.html, filed with the Fohlman Declaration as Exhibit I, which indicates that most microorganisms, including most viruses and all bacteria and fungi, are larger in size than 40 nm in diameter, many much larger, and that even those microorganisms that are not, namely a few types of viruses, are still at least 20 nm in diameter (see for example Paramyxovirus 0.022 μm coccus diameter). It can be appreciated from these references that the vast majority of microorganisms, including many types of viruses, could not conceivably be incorporated into an ISCOM particle because the microorganisms are larger than an ISCOM particle. *E.g.* Fohlman Declaration, para. 19. It can also be appreciated from these references that even those few types of microorganisms that are smaller than an ISCOM particle, namely certain types of viruses, are not sufficiently small to be able to be incorporated into an ISCOM particle. *E.g.* Fohlman Decl., para. 19. Briefly, non-amphipathic proteins cannot be encased within an ISCOM particle due to the small internal volume of the ISCOM particle, as indicated in the Barr reference, page 12. Viruses are larger than individual protein molecules generally. This is evident, among other reasons, because viruses comprise pluralities of protein molecules. Thus, it follows that viruses also cannot be encased within an ISCOM particle also due to size. Moreover, the structure of ISCOMs would also prevent incorporation of viruses. As indicated in a reference to Hu et al., Advanced Drug Delivery

Reviews (2001), 51, 149, 150, the current understanding of the structure of ISCOMs is that they exhibit icosahedral symmetry and are assembled from 12 morphological 10-12 nm subunits. Moreover, ISCOM particles have a relatively rigid structure, as noted in the Barr reference, page 11. A virus, even one as small in size as 20 nm, would be larger in size than the ISCOM subunits between which it would need to pass and thus would disrupt the icosahedral structure and inter-subunit interactions, all of which would prevent incorporation of the virus per se. Thus, for at least these reasons, it would be physically impossible to incorporate any structure as large as a microorganism into an ISCOM particle. Given that an ISCOM particle is too small for incorporation of a micro-organism per se, the terminology of Wechter regarding incorporation of a live attenuated virus into ISCOMs cannot be a teaching of incorporation of a live attenuated virus per se. For at least these reasons, Wechter fails to teach any composition that includes an iscom particle and a live virus, or any other live micro-organism, or any method of making such a composition.

ii. Incorporation of a microorganism per se into an ISCOM particle would require solubilization and thus killing of the microorganism prior to incorporation, given that methods actually known for incorporation of compounds or structures into ISCOMs are based on solubilization and given that solubilization of microorganisms results in killing of the microorganisms.

The terminology of Wechter regarding incorporation of a live attenuated virus into ISCOMs cannot be a teaching of incorporation of a live attenuated virus per se into an ISCOM particle, because methods actually known for incorporation of compounds or structures into

ISCOMs are incompatible with maintenance of the structural integrity of, let alone survival of, any microorganisms. More specifically, as indicated by the above-noted expert Fohlman, known methods for making ISCOM particles related to use of whole microorganisms are based on extraction of antigens from the whole microorganisms followed by incorporation of the antigens to yield ISCOM particles. Fohlman Declaration, para. 20. Corroborating evidence includes the above-mentioned Barr reference, pages 11-13, which provides a broad review of methods known in the art for incorporating cell-derived molecules and other compounds and structures into ISCOM particles. Briefly, all of the methods described therein that relate to whole microorganisms include a step of solubilization of the microorganisms for purposes of extraction of proteins and other antigenic molecules and structures therefrom. *E.g.* Fohlman Decl., para. 20, citing Barr reference, pages 11-13. Corroborating evidence also includes the results of the above-noted PubMed searches, corresponding to Exhibits D-F of the Fohlman Declaration, which failed to reveal methods for incorporation of live microorganisms per se. To be clear, not every solubilization method would necessarily work with every microorganism, but all known method for incorporation of antigens from any microorganism into an ISCOM particle involves a step of solubilizing the particular microorganism. Fohlman Declaration, para. 22, citing Fohlman reference, filed with Fohlman Declaration as Exhibit J.

The solubilization step of the above-noted methods would necessarily result in killing of the solubilized microorganism for at least the following reasons. First, the solubilization methods are designed particularly to remove surface antigens out of microbial structures, for example based on disruption of lipid membranes. Morein Decl., para. 10. Such removal results in destruction of the integrity of the surface of the microorganism, which is known to result in

killing of the microorganism. Consistent with such destruction, detergent plays the further role of dissolving phospholipids, Barr reference, pages 11, 13, a preferred component of ISCOMs generally and a necessary component when ISCOMs containing proteins are to be made, Barr reference, page 10, and also a component of membranes of microorganisms generally. Thus, the solubilization step results in killing of microorganisms. *E.g.* Fohlman Decl., para. 20. Second, consistency of the effects of adjuvants has long been a desirable goal of adjuvant research, and a solubilization method that did not kill the treated microorganism would not be expected to yield an adjuvant that could provide consistent effects. In support, the Barr reference, page 8, asks "[w]hy have adjuvants remained an unattractive area of investigation for large, well-funded research groups?" and then answers that "[o]ne major deterrent has been the general inconsistency of adjuvants." Third, safety is crucial regarding adjuvants, and a solubilization step that did not kill or otherwise remove the live organism prior to formation of iscom particles could have disastrous consequences if the resulting ISCOM particles were administered to non-immune animals or humans by causing rather than preventing infection. In support, the above-mentioned document titled Vaccine Development Overview states that "[t]he vaccine itself should produce only limited, if any, undesirable side effects," and that "[i]t also must not endanger its recipients . . . through danger of infection and adverse reaction." Although the Examiner has argued in the Advisory Action dated May 22, 2009 that Applicant has presented no evidence that solubilization would necessarily result in killing of cells, the role of detergent in the solubilization step and the evident desire for consistency and safety of adjuvants indicates otherwise.

Thus, for at least these reasons, the methods known in the art for incorporation of any

compounds or structures into ISCOMs would necessarily result in killing of the live microorganisms prior to any incorporation step. Given that methods actually known for incorporation of compounds or structures into ISCOMs are based on solubilization and given that solubilization results in killing of microorganisms, the terminology of Wechter regarding incorporation of a live attenuated virus into ISCOMs cannot be a teaching of incorporation of a live attenuated virus per se.

Thus, for at least the foregoing reasons, Wechter fails to teach any composition that includes an iscom particle and a live virus, or any other live micro-organism, or any method of making such a composition. In contrast, according to the present invention as claimed in claims 1, 2, 6, 9, 10, 15, and 21, an iscom particle or iscom matrix particle is mixed with a live micro-organism in a single composition. The rejection of claims 1 and 9 is therefore respectfully submitted to be overcome. Moreover, claims 2 and 6 both depend from claim 1 and claims 10, 15, and 21 depend from claim 9 and accordingly the rejection of these claims is also respectfully submitted to be overcome.

IV. REJECTIONS UNDER 35 U.S.C. § 103(a)

A. Rejection of claims 1, 2, 5-10, and 13-15 under 35 U.S.C. § 103(a) over Wechter in view of the Morein '354 patent

The Examiner has maintained the rejection of claims 1, 2, 5-10, and 13-15 under 35 U.S.C. § 103(a) as being unpatentable over Wechter in view of Morein et al. (U.S. Pat. No. 5,679,354). The Examiner has also extended the rejection to new claims 20 and 21 on the same grounds and to new claims 22 and 23, assuming that the claims read on embodiments wherein a single population of iscoms comprises more than one Fraction of Quil A, also on the same

grounds. Specifically, the Examiner has stated that "[w]hile Wechter teaches the incorporation of attenuated viruses into iscoms, it does not specify the formula of the iscoms." Office action dated July 28, 2008, p. 7. The Examiner then argued that "Morein provides teachings relating to iscoms for use as an adjuvant for antigens." Office action dated July 28, 2008, p. 7.

Respectfully, the incorporation of attenuated viruses into ISCOMs is not the same as making an antigenic composition by mixing an ISCOM and at least one live micro-organism. Specifically, for the reasons indicated above in section III, Wechter relates to incorporation of antigens derived based on solubilization, and thus killing, of a virus, not based on incorporation of a virus per se and, moreover, incorporation of a live or whole virus per se into an ISCOM particle is not technologically possible. Thus, as indicated above, Wechter does not teach any antigenic composition comprising an iscom and at least one live micro-organism.

The Morein '354 patent also does not teach such a composition. Specifically, the above-noted Inventor Morein has stated, based on his personal knowledge as an inventor of the Morein '354 patent, that "when the inventors of the '354 patent, including myself, indicated in the '354 patent that iscom matrix could be used as an adjuvant with whole organisms, we did not intend that Quillaja saponin and/or iscom matrix/iscom particles would be used with live whole microorganisms." Morein Decl., para. 17. As Morein notes, this is because, among other reasons, iscom particles were known to preferably be made with saponins, and saponins were known to have a particularly striking anti-microbial nature. This is shown, for example, in the Sparg reference, filed with the Morein Declaration as Exhibit B, which states that saponins have been reported to have antimicrobial activity. See also Morein Decl., paras. 14-15 (providing citations to scientific references to support the proposition that saponins were known to have antimicrobial and membrane-permeabilizing activity). As Morein also notes, given that saponins

were known to have negative effects against live microorganisms, saponins would have been expected to have particularly negative effects on live attenuated viruses. Morein Decl., para. 16. Although the Examiner argued in the Advisory Action dated May 22, 2009 that avoiding the cytolytic activity of saponins may have been partially a reason for incorporation of live attenuated viruses per se into iscoms, the incorporation process would still include exposure of the virus to saponins, thus defeating the purpose of avoiding the cytolytic activity of saponins. This is because known methods for incorporation of compounds or structures relating to micro-organisms into ISCOMs include the step of formation of ISCOMs particles from dissolved saponins, as shown for example in the above-mentioned Barr references, page 11.

Thus, the combination of Wechter and Morein does not make obvious the inventions as claimed in claims 1 and 9. For at least these reasons, the rejection of claims 1 and 9 is therefore respectfully submitted to be overcome. Moreover, claims 2, 5-8, 10, 13-15, and 20-23 depend from claims 1 or 9, either directly or indirectly, and accordingly the rejection of these claims is also respectfully submitted to be overcome.

B. Rejection of claims 7, 8, 13, 14, 22, and 23 under 35 U.S.C. § 103(a) over Wechter in view of the Morein '354 patent and Cox

The Examiner has maintained rejection of claims 7, 8, 13, and 14 under 35 U.S.C. § 103(a) as being unpatentable over Wechter in view of Morein as applied to claims 1, 2, 5, 6, 9, 10, 13, and 15, and further in view of Cox et al. (WO 96/11711). The Examiner has also extended the rejection to new claims 22 and 23. The rejection is impliedly based on an assumption that the combination of Wechter and Morein makes obvious an antigenic composition comprising an iscom and at least one live micro-organism. For the reasons

indicated above in section IV.A., the combination of Wechter and Morein does not make obvious such an antigenic composition. The rejection of claims 7, 13, 22, and 23 is therefore respectfully submitted to be overcome. Moreover, claims 8 and 14 depend from claims 7 and 13, respectfully, and accordingly the rejection of these claims is also respectfully submitted to be overcome.

C. Rejection of claims 1, 2, 4, 9, 10, 12, 15, and 18 under 35 U.S.C. § 103(a) over Van Woensel

The Examiner has maintained rejection of claims 1, 2, 4, 9, 10, 12, 15, and 18 under 35 U.S.C. § 103(a) as being unpatentable over Van Woensel et al. (U.S. Pat. No. 5,925,359). The Examiner has stated that "Van Woensel teaches a composition for the vaccination of pigs comprising live attenuate[d] PRRS viruses" and "that the composition[] may be combined with an adjuvant." Office action dated July 28, 2008, p. 8. The Examiner has also stated that the reference "specifically suggests the incorporation of the live vaccine antigens in iscoms." Office action dated July 28, 2008, p. 8. The Examiner has further stated that "the reference suggests the additional combination of live[] attenuated vaccines with other antigens, including antigenic material (i.e. antigenic molecules) from other pathogens." Office action dated July 28, 2008, p. 8. The Examiner has stated further still that "as with Wechter, the [Van Woensel] reference specifically indicates that either live (attenuated) or inactivated virus may be incorporated into the iscoms," and thus that "the reference indicates that the live viruses may be so incorporated." Office action dated December 17, 2008. Respectfully, as is the case with the Wechter reference, Van Woensel does not teach making a composition by mixing an iscom particle and at least one

live micro-organism, and thus Van Woensel does not make obvious the inventions as claimed in claims 1 and 9.

Specifically, as indicated by the above-noted Inventor Morein, although Van Woensel indicates that incorporation of antigens of a live attenuated virus is a possible way of adjuvation, a person of ordinary skill in the art would realize that Van Woensel does not disclose incorporation of a live attenuated virus into an ISCOM particle. Morein Declaration, para. 12. First, for the reasons argued above in section III.A. regarding the Wechter reference, and based on the evidence cited in that section, a person of ordinary skill in the art would understand the terminology used by Van Woensel, specifically that "[i]ncorporation of the antigens in Iscoms is also a possible way of adjuvation," to teach incorporation of antigens derived based on solubilization, and thus killing, of a virus, not incorporation of a live attenuated virus per se. Specifically, as discussed above with regard to terminology used in Wechter, terminology similar to that used in Van Woensel is understood in the art to refer to incorporation of antigens derived based on solubilization, and thus killing, of a virus, not based on incorporation of a virus per se. Moreover, as also discussed above, the scientific literature appears to contain no references purporting to explain, either in theory or practice, <u>how</u> a live virus or other micro-organism could be incorporated. Second, for the reasons argued above in section III.B., regarding the Wechter reference, and based on the evidence cited in that section, incorporation of a live or whole virus or other micro-organism into an ISCOM particle is not technologically possible, again due to the size of ISCOM particles and the solubilization step present in methods that are actually known in the art. The rejection of claims 1 and 9 is therefore respectfully submitted to be overcome. Moreover, claims 2, 4, 10, 12, 15, and 18 depend from claims 1 or 9, and accordingly the rejection of these claims is also respectfully submitted to be overcome.

D. Rejection of claims 5-8, 13-14, and 20-23 under 35 U.S.C. § 103(a) over Van Woensel in view of Cox

The Examiner has maintained rejection of claims 5-8 and 13-14 under 35 U.S.C. § 103(a) as being unpatentable over Van Woensel as applied to claims 1, 2, 4, 9, 10, 12, 15, and 18, and further in view of Cox et al (WO 96/11711). The Examiner has also extended the rejection to new claims 20-23. The Examiner has stated that "Van Woensel teaches compositions comprising an attenuated live virus and an iscom" and "that the compositions may comprise additional antigens." Office action dated July 28, 2008, p. 9. The Examiner has also stated that "Cox teaches that iscoms may be in the forms of iscoms comprising the glycosides and lipids identified in the rejected claims" and "that iscom matrices may be used which incorporate an immunogen." Office action dated July 28, 2008, p. 9. Respectfully, for the reasons argued above in section IV.C., Van Woensel does not teach a composition comprising an iscom particle and at least one live micro-organism, and neither does Cox. Thus, the combination of Van Woensel and Cox does not make obvious the inventions as claimed in claims 5-8, 13-14 and 20-23. The rejection of claims 5-8, 13-14, and 20-23 is therefore respectfully submitted to be overcome.

V. REQUEST THAT APPLICATION BE ALLOWED

In light of the foregoing, it is respectfully submitted that the present application is in condition for allowance and notice to that effect is hereby requested. If it is determined that the application is not in a condition for allowance, the Examiner is invited to initiate a telephone interview with the undersigned attorney to expedite prosecution of the present application.

If there are any additional fees resulting from this communication, please charge the same to our Deposit Account No. 16-0820, our Order No. ALBI-41848.

Respectfully submitted,
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